originally filed. Specifically, the reference to the endothelial glycoform of CD34 appears, for example, at page 3, line 14 of the specification. The recitation of a suitable pharmaceutically acceptable vehicle in claim 26 is supported, for example, at page 19, line 19.

The Objection and Rejections

Sections 2, 3, 4 and 5

In sections 2, 3, and 5 of the Office Action, applicants were requested to make certain formal changes in the specification. The foregoing amendments are believed to be fully responsive to these objections. Applicants note the requirement for corrected formal drawings (section 4 of the Office Action), but elect to postpone the filing of formal drawings until after the receipt of a Notice of Allowance in connection with the present application.

Sections 6 and 7

Claims 1-14 and 26-27 were rejected under 35 U.S.C. §112, first paragraph, as "the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention."

A) According to the Examiner, applicants did not disclose how to use the CD34-specific pharmaceutical compositions, alone or in combination with other ingredients, for the treatment of the indicated pathological conditions. The following specific statements are made in this rejection.

(a) Pharmaceutical therapies are unpredictable in the absence of *in vivo* clinical data.

(b) *In vitro* and animal model studies do not correlate well with *in vivo* clinical results in patients.

(c) The mouse experiments disclosed are not sufficient to establish a nexus with modulating human disease through L-selectin-CD34 interactions.

(d) It is unclear from the specification whether the human L-selectin-CD34 interaction is key to human leukocyte-endothelial cell interaction. As human leukocyte-mediate inflammation may operate through other known adhesion pathways, the specification fails to enable the critical role of targeting CD34 in inhibiting human disease.

(e) It is unclear what are the specificities on human CD34 cells which result in

inhibition of human leukocyte-endothelial cell interactions.

(f) Relying on various publications (Harlan, Ward *et al.*, McMurray *et al.*, Albelda *et al.*), the Examiner points out that finding is mouse models are not necessarily indicative of human utility of adhesion molecules; and specifically, that the utility of antibodies is questionable.

The Examiner concludes that in view of the "lack of predictability of the art to which the invention pertains" undue experimentation would be required to practice the claimed method with a reasonable expectation of success.

The cancellation of claims 2-6, 13, 14 and 27 moots their rejection. The rejection of the remaining claims is believed to be misplaced and is respectfully traversed.

It is noted that the claims were not rejected for lack of utility under 35 U.S.C. §101, it is therefore deemed to be established that the present invention is useful for the treatment of pathological conditions mediated by L-selectin. It is submitted that the practice of the invention by those skilled in the art, based upon the disclosure of the present application and general knowledge in the pertinent art, does not require undue experimentation.

The claims, as currently amended, concern the use of an isolated and purified CD34 polypeptide for treating a pathological condition associated with the L-selectin mediated adhesion of leukocytes to endothelial cells. Accordingly, the Examiner's concerns about the viability of peptide- or antibody-based therapy (e.g., Harlan et al., Ward et al.) are no longer relevant.

The Examiner's other major concern, the lack of actual data supporting the criticality of L-selectin-CD34 interactions in humans, is also believed to be misplaced. CD 34 has been isolated from **human** tonsil, and has been demonstrated to play an important role in mediating lymphocyte tethering, rolling, and resistance to detachment in shear. (Puri et al., J. of Cell. Biology 131, 261-270 (1995) - copy enclosed.) According to the authors' conclusions, "[human] CD34 is the predominant L-selectin ligand in the mixture of peripheral node addressins from human tonsil."

As far as the human therapeutic use of CD34 in general is concerned, the significance of L-selectin in the clinical condition of rheumatoid arthritis (RA), a chronic inflammatory disease, has been demonstrated by clinical test involving human RA patients. Kurohori et al., Clinical rheumatology 14, 335-341 (1995) (copy enclosed), have shown that there is a positive

correlation between the expression of L-selectin on peripheral blood mononuclear cells of human RA patients and disease activity. The state of disease activity in thirty three (33) human patients and eleven (11) normal controls used in the study, was assayed according to values of the erythrocyte sedimentation rate (ESR), and joint scores representing the patients' clinical activities. The authors found that:

> "The most striking difference between RA patients and normal controls was with respect to the expression of L-selectin, as compared to the other adhesion molecules." (Page 340, first column.)
>
> "In the present study, there were positive correlations between the number of L-selectin positive cells and laboratory data such as ESR, CRP [C-reactive protein], suggesting that the expression of L-selectin reflects the activity of inflammation of RA." (Page 340, second column.)
>
> "The importance of the adhesion molecules in PBMC from RA patients might be especially stressed in the rolling step of active inflammation." (Page 340, second column.)
>
> The authors conclude that "L-selectin may be the most important and valuable adhesion molecule on PBMC to analyze the pathologic process of RA."

As CD34 has been linked to lymphocyte migration in humans, and has been identified as the physiologically significant ligand for L-selectin (Baumheuter et al., Blood, 84 2554-2565 (1994) - copy enclosed), one of ordinary skill in the art could practice the present invention with a reasonable expectation of success, without undue experimentation.

The Examiner suggests that L-selectin might not be equally suitable for the treatment of all acute and chronic inflammatory conditions. The Examiner will, of course, realize that even if there might be some embodiments within the scope of the claims that are less effective, or do not work at all, their existence would not jeopardize the validity of generic claims. Furthermore, the claims permit the use of L-selectin in combination with other adhesion molecules, and such combination therapy might be effective when the efficacy of L-selectin alone is not satisfactory. While the finding of a certain combination particularly suited for the treatment of a certain inflammatory condition might involve some experimentation, this would not bar the patentability of the present invention. Absolute predictability is not a requirement for enablement.

Turning to the specific references, cited in support of this rejection, the Edgington paper

is believed to be of no relevance, since it was published before the identification of CD34 as the biologically more relevant L-selectin ligand by the present inventors. Indeed, Edgington is very complimentary about the earlier discovery by the Lasky and Rosen research group of another L-selectin ligand, GlyCAM-1. In the concluding sentence of his paper, the author notes that "[a]s these structures gain names and identified, dial-in selectin inhibition may emerge as a reality." Edgington was unable to express any views about the significance of identifying CD34 as a major L-selectin ligand, since the present discovery was make subsequent to the publication of his review article.

Ward et al. does not discuss the use of protein ligands of adhesion molecules, e.g. L-selectin, as blocking agents. The focus of the paper is on the use of blocking antibodies and antibody-like immunoadhesin molecules, along with cytokine inhibitors. Indeed, the approaches proposed for the *in vivo* blocking of adhesion molecules are limited to the use of monoclonal antibodies, peptide mimics, selectin-Ig chimeras (antibody-like immunoadhesins), oligosaccharides and cytokine blockade. As the use of native ligands of selectins or other adhesion molecule is not contemplated in this paper, it has no direct bearing on the method disclosed and claimed in the present application.

Hemmerich *et* al. propose that the mucin domains present in the two known L-selectin ligands, CD34, GlyCAM-1, and MadCAM, play an important role in the multivalent presentation of carbohydrate chains which, in turn, are an important feature for the activity of these ligands. As the claims, as amended, concern the use of a CD34 glycoprotein corresponding to the endothelial glycoform of native CD34, they reflect the importance of the carbohydrate structure in the biological activity of CD34.

The data cited from the McMurray review article concern the use of anti-L-selectin antibodies. As the carbohydrate structure of L-selectin and the L-selectin ligands has been identified as crucial for mediating biological activity, and it is well known that anti-carbohydrate antibodies often lack specificity and are usually of relatively low avidity (see, e.g. Baumheuter, *supra*, page 2564, first column), the problems experienced with the use of anti-L-selectin antibodies are not surprising. One would not expect similar difficulties with the use of an isolated and purified CD34 polypeptide, having the carbohydrate structure of a native endothelial CD34 molecule.

Similarly, Albelda *et al.* concern the limitations of antibody therapy, and is, therefore,

not relevant to the current claims. There is absolutely no disclosure or hint in this reference that would question the therapeutic potential of glycoprotein ligands of L-selectin (or any other selectin).

In view of the foregoing arguments and evidence, the reconsideration and withdrawal of this rejection if respectfully requested.

B) Claim 9 was found to be unduly broad in its recitation of the compounds which may be used in addition to the CD34 glycoprotein in the practice of the present invention. Without acquiescence in the Examiner's position, the reference to a non-protein antagonist has been deleted. It is submitted that the use of the remaining polypeptides and antibodies recited in the claim are clearly enabled. The terms "selectin", "selectin ligand", "integrin" and "integrin ligand" are well known in the art, as attested by the references of record, including publications cited by the Examiner in other sections of the Office Action. In addition, such receptors and their ligands are specifically enlisted in the paragraph bridging pages 18 and 19 of the specification. What claim 9 says is that, in view of the known overlaps in the biological activities of certain selectins and integrins, the efficacy of CD34 therapy may be enhanced by the use of additional selectins and integrins, or their ligands. As these molecules are known in the art, along with their biological activities, their use in the method of the present invention does not require undue experimentation.

C) The specification was objected to and claim 14 was rejected under 35 U.S.C. §112, first paragraph for alleged lack of adequate written description. Without acquiescence in the Examiner's position, claim 14 has been cancelled, which moots its rejection.

Section 8

Claim 9(g) was rejected under 35 U.S.C. §112, first and second paragraphs for alleged lack of enablement and indefiniteness. As this section of claim 9 has been cancelled, the rejection is moot.

Section 9

Claims 1-3, 9-14 and 26-27 were rejected under 35 U.S.C. §112, second paragraph, as "being indefinite."

A) Claims 1-3, 9-14 were found to be indefinite in the recitation of "inhibiting a

pathological condition associated with intracellular adhesion mediated by L-selectin." As claims 2, 3 and 14 have been cancelled, and the remaining claims are directed to L-selectin mediated inflammations, the withdrawal of this rejection would be in order.

B) Claims 3-4 were found indefinite for their use of the language "endothelial cells on peripheral or mesentric lymph nodes." The cancellation of these claims moots their rejection.

C) Claim 14 was found indefinite in its reference to MECA-79. As claim 14 is now cancelled, its rejection should be withdrawn.

D) Claim 13 was found to be indefinite in its reference to "a pharmaceutically active compound." The cancellation of this claim moots its rejection.

E) and F) Claims 26-27 were rejected as indefinite in their recitation of a "composition". Claim 27 was additionally rejected for its reference to "an additional pharmaceutically active compound." The cancellation of claim 27 and the amendment of claim 26 are believed to overcome this rejection.

G) As noted before, the amendments in the claims are fully supported in the specification, without adding new matter.

Section 12

Claims 1-8, 12-14 and 26-27 were rejected under 35 U.S.C. § 102(e) as "anticipated by or, in the alternative, under 35 U.S.C. §103 as obvious over Butcher et al. (U.S. Patent No. 5,538,724)." Claims 2-6, 14 and 27 have been cancelled, the rejection of the remaining claims is respectfully traversed.

Butcher et al. teach the use of MECA-79 antibody. The claims in the present application are now directed to the use of a particular glycoform of CD34 polypeptide. Accordingly, Butcher et al. does not anticipate the present invention. Nor does it render obvious the invention claimed. It is well established that the use of antibodies in therapy raises difficulties not associated with the use of polypeptide ligands, like the one recited in the present claims. Accordingly, the reconsideration and withdrawal of this rejection is respectfully requested.

Section 13

Claims 1-8, 12-14 and 26-27 were rejected under 35 U.S.C.§102(e) as "anticipated by"

or, in the alternative, under 35 U.S.C. §103 "as obvious over" Lasky *et al.* (U.S. Patent No. 5,304,640). According to the rejection, the "instant claims are drawn to the use of CD34-specific antagonists in therapeutic methods, and compositions comprising said CD34 antagonists." Lasky *et al.* was cited for its teaching of the use of L-selectin ligand Sgp90 antagonists to treat inflammatory conditions. Specific reference was made to Section K. Therapeutic Compositions, in the cited patent. While the Examiner admitted that "the reference is silent about the CD34 specificity", he contended that "Sgp90 and MECA-79 are the same as the claimed CD34 specificity." The Examiner cited In re Best, In re Marosi and Ex parte Novitski in support of the position that it "is the burden of the applicant to show the unobvious difference between the claimed and disclosed methods and compositions."

Claims 2-6, 14 and 27 have been cancelled. The rejection of the remaining claims is respectfully traversed.

The invention as claimed in original claims 1-14, 26 and 27 was directed to the treatment of L-selectin-mediated conditions by using an isolated, purified CD34 polypeptide, or an anti-CD34 antibody, and not to the use of CD34-specific antagonists in general. Upon entry of the current amendment, the invention will be specifically directed to the use of an isolated and purified CD34 polypeptide corresponding to the glycoform of endothelial CD34 for the treatment of L-selectin-mediated inflammation.

The present inventors have, indeed, found that the non-purified 90 kD murine protein, referred to as Sgp90 in the Lasky *et al.* patent, is substantially identical with murine CD34, which was a known protein of unknown function prior to the present invention. Although the Lasky *et al.* patent suggests the use of selectin ligands to block the binding of a corresponding selectin receptor to its native ligand, in order to treat a symptom or condition associated with excessive binding of circulating leukocytes to endothelial cells, this should not bar the issuance of a patent on the present invention. The focus in the Lasky et al. patent is on the L-selectin ligand, GlyCAM-1. The specific role of the 90 kD murine protein in L-selectin mediated adhesion (more specifically, inflammatory) events is not disclosed in this patent. Indeed, at the priority date of Lasky et al. (5,304,640), there were major doubts about the role, if any, played by the 90-kD molecule in L-selectin-mediated inflammatory events. Applicants refer to the disclosure of Lasky et al. (CSHQB), which was cited in Section 14 of the present Office Action. From applicants' analysis of the latter Lasky et al. publication in response to the Section 14

rejection it should be apparent that the actual biological role of the 90-kD ligand was not determined until the present inventions was made. Without this information, and especially without the recognition of the role played by the carbohydrate structure of the endothelial glycoform of CD34 in L-selectin-associated inflammatory conditions, a person skilled in the art could not have arrived at the invention claimed in the present application.

Although the present invention is believed to be unobvious over the Lasky et al. patent (5,340,640), applicants note that the Lasky *et al.* patent issued on April 19, 1994, which is subsequent to the earliest priority date (May 3, 1993), and less than one year before the actual filing date of the present application (July 11, 1994), and discloses but does not claim the therapeutic use of selectin ligands. Three of the four inventors of the Lasky *et al.* patent (Laurence A. Lasky, Steven D. Rosen and Mark S. Singer) are also named as inventors in the present application. Should the present rejection be repeated, as it should not be, applicants are able to file a Declaration under 37 C.F.R. 1.132 by the three common inventors of the Lasky *et al.* patent and the present application contains an unequivocal statement that the invention of using Sgp90 for the treatment of symptoms or conditions associated with the excessive binding of circulating leukocytes to endothelial cells, as disclosed in U.S. Patent No. 5,304,640 (Lasky *et al.*) was conceived them. In re DeBaun, 214 USPQ 933 (CCPA 1982). Such a Declaration would render the invention, as disclosed in the Lasky *et al.* patent, unavailable as prior art under 35 U.S.C. §102(e). It is noted that the experiments performed by Susanne Beumheuter were critical for determining that Sgp90 and CD34 were identical, and to demonstrate that CD34 is a selectin ligand, accordingly, she is correctly named as an inventor in the present application.

Section 14

Claims 1-14 and 26-27 were rejected under 35 U.S.C. §103 as obvious over a combination of Lasky et al. (5,304,640) or Butcher et al. with Lasky et al. (CSHSQB), Berg et al., or Imai et al., Sutherland et al., Lasky et al. (5,098,833), Watson et al., Fina et al.

The rejection of claims 2-6, 14 and 27 is mooted by their cancellation. The rejection of the remaining claims is believed to be unfounded, and is respectfully traversed.

The primary Lasky et al. reference is not available as prior art for reasons set forth in response to the previous rejection. Accordingly, its combination with any and all of the

secondary references, which do not make up for the lack of the primary reference, falls.

Butcher et al. was cited for its disclosure of the MECA-79 antibody. As the present claims do not recite the use of antibodies, this teaching is irrelevant. Similarly, the teaching of the secondary references, so long as it is directed to the use of anti-L-selectin antibodies, no longer pertains to the claims pending in this application.

Although CD34 was known in the art before the priority date of the present application, its function as a biologically relevant L-selectin ligand was highly unexpected in view of its broad distribution on extra-lymphoid endothelial cells, which were earlier thought not to express ligands for L-selectin.

The Lasky et al. publication (CSHQB), focuses on the identification of GlyCAM-1 as an L-selectin ligand. The authors are uncertain about the nature and function of the 90-kD molecule, now known to be CD34. For example, according to the teaching on page 266, first column, the authors

> "can only speculate on the physiological role of the 90-kD ligand versus GLYCAM 1. One possibility is that the 90-kD ligand is the transmembrane molecule which binds GLYCAM 1 to the endothelial cell surface. . . A second possibility is that shed GLYCAM 1 performs other physiological roles, such as lymphocyte activation or chemotaxis, whereas the 90-kD ligand is the actual HEV adhesive ligand for lymphocyte trafficking. An argument against this proposition is that staining of HEV with the antisera against GLYCAM 1 peptides reveals a luminal staining pattern. . . as would be expected for an adhesive ligand such as GLYCAM 1. A final possibility is that both GLYCAM 1 and the 90-kD ligand act as adhesive molecules, but the 90-kD ligand may act as an "inflammation-specific" ligand, whereas GLYCAM 1 may be specific for peripheral lymph node HEV trafficking."

Accordingly, the authors had at least three different hypotheses about the biological function of the 90-kD molecule, and there is nothing in the prior art that would have suggested to prefer one of these theories over the other two. It is only the teaching of the present invention that identifies the real biological significance and role of the 90-kD CD34 L-selectin ligand, which is, of course, not available as prior art. As the present inventors do not claim the sequence of the 90-kD ligand, it is irrelevant whether its sequence could have been determined without undue experimentation. The present invention is not limited to the identification of the 90-kD molecule as CD34. An integral part of the present invention is the determination of the biological role of CD34 in the mediation of L-selectin-associated inflammatory conditions, and the identification of the role played by the carbohydrate structure in this activity. This

invention is not disclosed in Lasky et al. (CSHQB) or in any of the other secondary references, such as Sutherland et al., Lasky et al. (5,098,833), Fina et al., Schlingemann et al.). Indeed, the teachings of the latter secondary references are even less specific than the Lasky et al. CSHQB publication.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Section 15

Claims 9-11 were rejected under 35 U.S.C. §103, "as being unpatentable" over the same combination of references as those used in the previous rejection, and further in view of Spertini et al., Carlos et al., Heavner et al. and Butcher et al. The basis for this rejection apparently is that the use of CD-34-specific reagents in combination with other antiinflammatory agents was suggested by prior art. Without conceding that this is the case, it is submitted that as claim 1, on which claims 9-11 depend, is patentable, there is no need for the dependant claims to exhibit any additional patentable feature. Accordingly, the withdrawal of this rejection is respectfully requested.

It is believed that the present application is in prima facie condition for allowance, and an early action to that effect is respectfully requested.

Respectfully submitted,
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